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Synthesis of Difluoromethyl and Monofluoromethyl Ketones for Biological Evaluation at the GABA-b Receptor

Mallory Maier

University of Mississippi. Sally McDonnell Barksdale Honors College

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SYNTHESIS OF DIFLUOROMETHYL AND MONOFLUOROMETHYL KETONES
FOR BIOLOGICAL EVALUATION AT THE GABA_B RECEPTOR

by
Mallory Maier

A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of
the requirements of the Sally McDonnell Barksdale Honors College.

Oxford, MS
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Approved by

Advisor: Professor David A. Colby

Reader: Tracy A. Brooks

Reader: Kristie Willett

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ABSTRACT

MALLORY MAIER: Synthesis of Difluoromethyl and Monofluoromethyl Ketones for Biological Evaluation at the GABA_B Receptor
(Under the direction of David A. Colby)

The central nervous system communicates using neurotransmitters. Most are excitatory neurotransmitters, such as acetylcholine, dopamine, and serotonin, but γ -aminobutyric acid (GABA) is the primary inhibitory neurotransmitter. There are two main types of GABA receptors. The GABA_A receptors are ion channels and are targeted by many drugs. However, there is a specific interest in developing compounds to interact with GABA_B receptors due to potential use as addiction treatments. There is currently only one FDA approved drug on the market, a muscle relaxer called baclofen, that selectively binds to GABA_B receptors. The goal of this project was to synthesize fluorinated compounds to be evaluated at the GABA_B receptor. The incorporation of fluorine into organic molecules is becoming increasingly important in the pharmaceutical industry. Specifically, fluorinated ketones are an important functional group in medicinal chemistry, but existing methods to synthesize this functional group are low yielding. A new method has been developed to access difluoromethyl ketones through the release of trifluoroacetate, and some of these molecules have been shown to serve as agonists of the GABA_B receptor. My project is the modification of this method to generate monofluoromethyl ketones to be submitted for biological evaluation at the GABA_B receptor.

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LIST OF ABBREVIATIONS

CNS	central nervous system
GABA	γ -aminobutyric acid
GERD	gastroesophageal reflux disease
Ser	serine
Asp	aspartic acid
TLC	thin layer chromatography
NMR	nuclear magnetic resonance spectroscopy
cAMP	cyclic adenosine monophosphate

1. Introduction

1.1 *Communication in the Central Nervous System*

Neurons, the functional cells of the central nervous system (CNS), communicate through impulses that release neurotransmitters resulting in either the excitation or inhibition of the post-synaptic cell. Neurons consist of three primary parts: the cell body, dendrites, and the axon. These structures form synapses with other neurons or receptors during neurotransmission. Dendrites are short arms on the nerve cell that conduct information toward the cell body. The axon extends from the cell body, and the terminal end forms a synapse with other neurons or receptor cells. The axon conducts nerve impulses from the cell body, called action potentials, to the terminal end.

When the action potential reaches the terminus of the axon, the neuron communicates with the postsynaptic cell through either an electrical or a chemical signal. Chemical synapses are most commonly found in the CNS. When the action potential reaches the terminal of the axon, it signals the release of chemical messengers called neurotransmitters. Neurotransmitters are released from the axon into the synapse, and they bind to their receptors on the membrane of the postsynaptic cell.

Neurotransmitters are synthesized and stored in the axon terminal in synaptic vesicles. When the action potential reaches the terminal, it causes the

vesicles to move to the membrane and release the neurotransmitters into the synapse. There are various physiological processes in place to remove the neurotransmitters from the synapse to maintain precise control of neural transmission. These processes include reuptake of the neurotransmitter by the axon, metabolism of the neurotransmitter, or diffusion into intercellular fluid resulting in decreased concentration.

There are two types of chemical synapses: excitatory and inhibitory. In an excitatory synapse, when the neurotransmitter binds to its receptor on the postsynaptic membrane, it results in the depolarization of the postsynaptic membrane resulting in the continuation of an action potential. The binding of neurotransmitters in an inhibitory synapse reduces the postsynaptic cell's ability to generate an action potential. This effect is generally accomplished by hyperpolarizing the postsynaptic membrane, making it more permeable to potassium and/or chloride ions, and less likely to depolarize.

1.2 *GABA*

Most neurotransmitters in the CNS are excitatory. The primary inhibitory neurotransmitter in the CNS is γ -aminobutyric acid (GABA). Its major roles are to regulate the excitation of neurons as well as regulate the release of other neurotransmitters.² There are two major types of GABA receptors that determine the actions of GABA: GABA_A and GABA_B. GABA receptors are a long-standing target in the pharmaceutical industry.

1.2.1 *GABA_A Receptors*

GABA_A receptors are pentamers consisting of two identical α subunits, two identical β subunits and one “other” subunit assembled around a central pore. Sixteen subunits have been identified that make up GABA_A receptors. The receptors are ligand-gated chloride-ion channels that suppress excitation in neurons.³ When GABA binds to the GABA_A receptor, it increases the cells permeability to chloride which reduces the cells ability to generate an action potential.⁴

GABA_A receptors are the most therapeutically targeted GABA receptor. There are three major classes of pharmaceuticals that target GABA_A receptors: barbituates, benzodiazepines, and non-benzodiazepines.⁵ These drugs treat various disease states including anxiety, insomnia, seizures and muscle spasms.

1.2.2 *GABA_B Receptors*

GABA_B receptors are heterodimeric, G-protein coupled receptors. The dimer is made up of GABA_{B1}, which contains the GABA binding regions, and GABA_{B2}, which activates the G-protein.⁶ These receptors inhibit the release of several neurotransmitters including acetylcholine, serotonin, dopamine, and noradrenaline through G-protein-dependent inhibition of voltage-gated calcium channels.⁷ They can also reduce neuronal excitation through activation of G-protein regulated potassium channels, and regulate intracellular signaling through inhibition of adenylyl cyclase activity.^{7,8}

GABA_B receptors can be linked to the pathophysiology of many CNS diseases and disorders such as anxiety, depression, autism spectrum disorders, stroke, drug addiction, Huntington's disease, Parkinson's disease and Alzheimer's disease. They can also be linked to muscle spasticity disorders, pain and gastroesophageal reflux disease (GERD).³ Unlike GABA_A receptors, there are few pharmaceuticals that target GABA_B receptors. Implications of targeting the GABA_B receptor include treatment of anxiety, mood disorders, and addiction to alcohol, cocaine, heroin, and nicotine. There remains a great deal of potential in the pharmaceutical industry to create drugs that target GABA_B receptors.

1.3 *Baclofen and Other GABA_B Agonists*

Currently, baclofen, a muscle relaxant, is the only FDA approved drug that targets the GABA_B receptor.³ The structure of GABA is imbedded in the structure of baclofen (Figure 1). Baclofen is used primarily to treat muscle spasms in patients with multiple sclerosis or spinal cord injuries. However, baclofen has been shown to be effective in off-label treatment and possible treatment of various ailments caused in part by pathogenesis of the GABA_B receptor pathway, such as GERD⁹, nicotine addiction, and post-traumatic stress disorder¹⁰. Despite its exclusivity as the only FDA approved GABA_B agonist drug, baclofen is far from ideal. Baclofen has low penetration into the brain, a narrow therapeutic window, short duration of action and a rapid tolerance.^{11,12} The development of GABA_B agonists that could overcome these barriers would be a substantial improvement over baclofen.

Previous research has shown that making even subtle changes to the structure of baclofen can produce antagonists, eliminate activity at the GABA_B receptor altogether, or even cause the compound to interact with other GABA receptors.³ Baclofen derivatives with structural modifications at the 3-position are GABA_B agonists.² For example, 3-aminopropyl phosphinic acid has been demonstrated to be a potential inhibitor of GERD, muscle relaxant and treatment for addiction.¹³

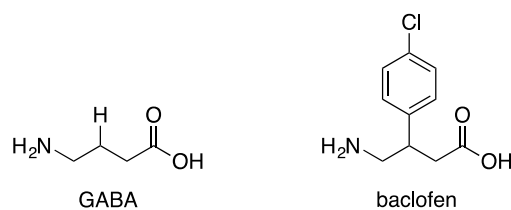


Figure 1 Structures of GABA and baclofen

1.4 *Fluorine and Medicinal Chemistry*

Incorporation of fluorine into organic compounds has become increasingly important in pharmaceuticals. Over the past several decades, 5–15% of the total number of new drugs launched worldwide were fluorinated.¹⁴ Fluorine is the most electronegative element which gives it certain inherent properties. Incorporating fluorine into drug molecules affects the pK_a of the drug and can influence certain characteristics such as solubility, permeability and protein binding of the drug.¹⁵ These characteristics, in turn, affect the absorption, distribution, metabolism and elimination of the drug. There are many examples of molecules where fluorine effectively replaced hydrogen or oxygen and maintained comparable activities at the site of action for the drug.¹⁴

Fluorine increases the permeability of a drug, which means it is more able to pass through a cell membrane. As the lipophilicity of a drug increases, likewise, the permeability of the drug increases.¹⁵ The lipophilicity of drugs is measured and reported as log P values, with a lower log P value being associated with higher lipophilicity.¹⁵ Mono- and di-fluorination of molecules have been shown to result in significant reductions of log P values for drugs.¹⁵ By increasing permeability of a drug, it simultaneously increases the bioavailability of the drug.

This improvement is of great importance when developing new drugs, especially those that must cross the blood-brain barrier.

2. Results and Discussion

2.1 *Synthesis of Difluoromethyl Ketones*

While there is not much data on the structure of the GABA_B receptor, it is known that two key active-site residues include Ser246 and Asp471. These residues have critical interactions with baclofen and GABA.¹⁶ The carboxylate of baclofen interacts with the serine residue of the GABA_B receptor, which led researchers to believe that α -fluorinated ketones might interact similarly due to their ability to form hemiketals with serine residues in an active site and serve as surrogates for carboxylic acids and phosphinic acids.²

Difluoromethyl ketones were synthesized because of the ketone's ability to revert to a gem diol in water (Figure 2) which increases its solubility and affords a tetrahedral shape, which can enable activity as a transition state mimic.¹ The difluoromethyl-starting material was synthesized from (Z)-4,4,4-trifluoro-3-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one and selectfluor under anhydrous conditions (see experimental details). A novel method has been discovered that was used to assemble the difluoromethyl ketones by aldol reactions with difluoroenolates following the release of trifluoroacetate in the presence of triethylamine (Figure 3).¹⁷ Once trifluoroacetate is released, the aldol reaction is rapid, resulting in the enolate attacking the electrophilic carbon of the aldehyde (Figure 3). Following an aqueous workup, the desired difluoromethyl ketone is obtained.

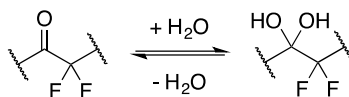


Figure 2 Ketone reverts to gem diol in presence of water

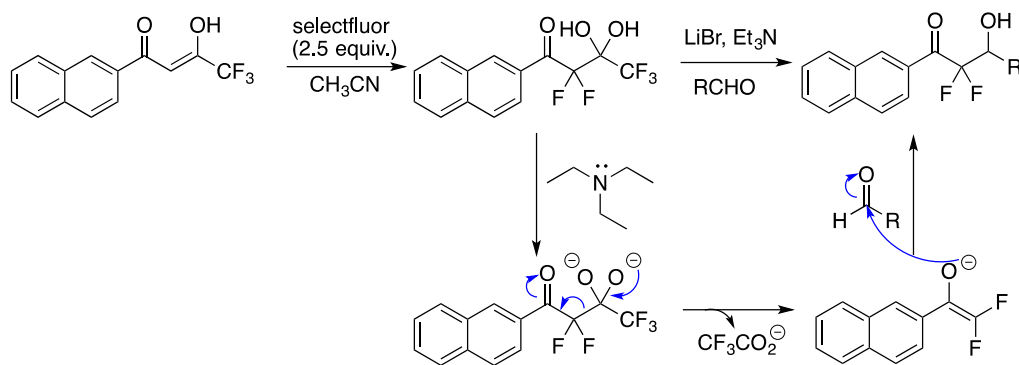


Figure 3 Difluoromethyl ketone from trifluoroacetate release and aldol addition

Unlike many other routes for fluorochemical synthesis, this approach yields difluoromethyl ketones in three synthetic steps with a high yield. The method is also versatile and can be used with many different ketones.² Using this approach, four difluoromethyl ketones were synthesized to reproduce reported procedures in the literature, as well as to learn the methods and techniques of synthesizing these compounds (Figure 4). Each compound was obtained in good yield and purified by silica flash chromatography. The reaction with cyclohexylcarbaldehyde required a lower temperature to achieve an acceptable yield. Each of these compounds were submitted for biological evaluation.

2.2 Synthesis of Monofluoromethyl Ketones

It is reported in the literature that difluoromethyl ketones show activity at the GABA_B receptor.² The goal of this project was to find out what, if any, activity monofluoromethyl ketones have at the GABA_B receptor. Another goal was to compare how the activity of monofluoromethyl ketones compare to the reported activity of difluoromethyl ketones.

The general synthesis of monofluoromethyl ketones is very similar to that of difluoromethyl ketones, with one key difference. The starting material was

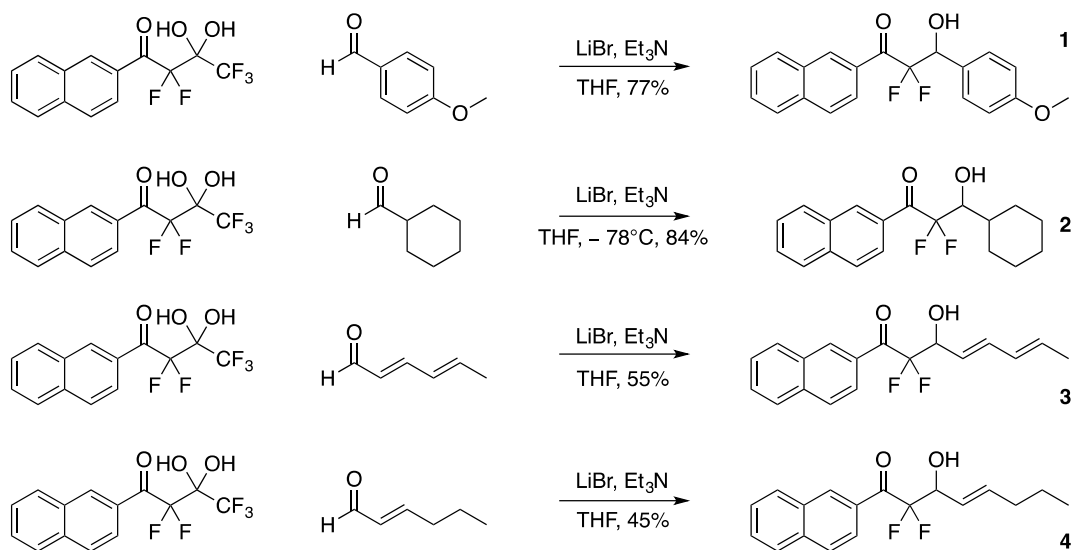


Figure 4 Synthesis of difluoromethyl ketones **1–4**

synthesized from reacting (Z)-4,4,4-trifluoro-3-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one with selectfluor in the presence of water, which lead to monofluorination of the compound (Figure 5). The mechanisms and reaction conditions involving trifluoroacetate release and the aldol additions remained the same. The same four aldehydes used in the difluoromethyl ketones syntheses were used in the monofluoromethyl ketone syntheses (Figure 6).

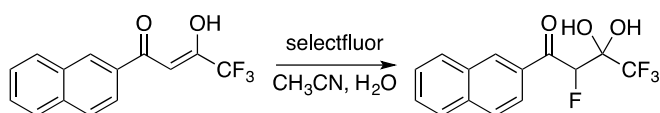


Figure 5 Monofluorination of starting material

2.3 Identification and Purification of Difluoromethyl Ketones and Monofluoromethyl

Ketones

Two primary techniques were used to identify compounds in the synthesis of both the difluoromethyl ketones and the monofluoromethyl ketones: thin layer chromatography (TLC) and nuclear magnetic resonance spectroscopy (NMR). TLC



TLC was also used to optimize solvent systems for the purification of the products using flash column chromatography, as well as to assist in collection of the products. The solvents used to purify the difluoromethyl ketones, as reported in the literature, resulted in the successful separation and purification of compounds at relatively high yields. When trying to duplicate purification procedures for the monofluoromethyl ketones, separation was not ideal. The solvent systems had to be optimized for each monofluoromethyl compound based on the polarity of the compound and the starting materials (see experimental details).

Once the compounds had been purified using flash column chromatography, NMR data was analyzed to confirm the purity of the compound. Proton NMR was used to determine if any non-fluorinated starting materials, or other impurities, remained with the product. Impurities contaminating the desired compounds could have lead to inaccurate results in biological testing of the activity of the compound at the GABA_B receptor. Fluorine NMR was used to verify that the starting material was not present, and that the correct number of fluorines were present on the desired compound. This data was especially important for the monofluoromethyl ketones to make sure that the difluoromethyl ketones were not present, because difluoromethyl ketones could alter the results of biological testing. Since it is already known that difluoromethyl ketones are active at the GABA_B receptor, a mixture of difluoromethyl and monoflouomethyl ketones could lead to false biological activity results.

2.4 *Biological Evaluation at the GABA_B Receptor*

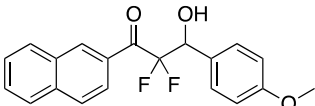
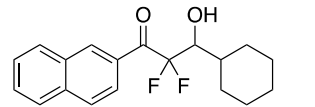
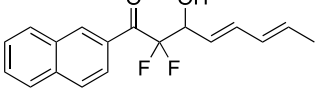
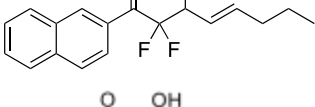
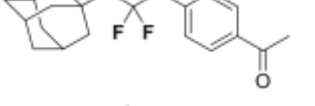
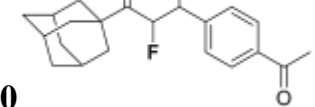
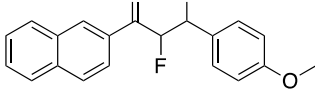
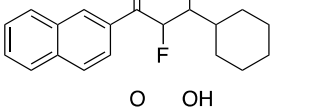
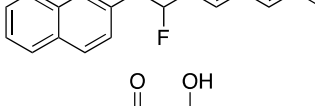
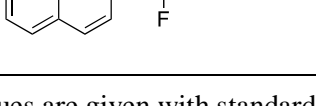
Biological evaluation of GABA, baclofen, and difluoromethyl ketones was performed to measure selectivity and potency at the GABA_A and GABA_B receptors, and the values were reported (Table 1).² GABA_B agonist activity was measured using a cell line expressing subunits of the human GABA_B receptor that when activated, inhibits the production of cAMP.² In the assay, forskolin, an activator of adenylyl cyclase, was used to stimulate cAMP production. Inhibition of forskolin-stimulated accumulation of cAMP was measured and reported.²

Baclofen and GABA were used as positive controls in the assay, and the results were comparable to other reported EC₅₀ values in the literature.² The lower the EC₅₀

value, the more potent the compound is at the receptor. Based on the values reported in Table 1, the difluoromethyl ketones synthesized show significant activity and selectivity at the GABA_B receptor. Although compound **9** was not synthesized in this project, it shows the greatest potency at the GABA_B receptor.

The goal of this project was to determine how the biologic activity of monofluoromethyl ketones compares to that of baclofen, GABA and the difluoromethyl ketones. Compound **10** (Table 1), was synthesized and tested by another member of David Colby's lab at the University of Mississippi, and it is reported that it showed a greater potency at the GABA_B receptor than its difluoro-analog. These data drive the need to determine whether all monofluoromethyl ketones would show greater potency at the GABA_B receptor over difluoromethyl ketones. Compounds **5–8** have been submitted for biological evaluation, but no data has been received. It is not known why the monofluorinated compound **10** exhibits greater activity than the difluorinated compound **9**.

Table 1 Biologic activity at the GABA_B receptor

<i>Compound</i>	<i>GABA_B EC₅₀ (μM)^a</i>	<i>GABA_A EC₅₀ (μM)^a</i>
GABA	0.53 ± 0.33	>100 ^b
Baclofen	1.7 ± 0.10 ^b	2.30 ± 0.59 ^b
1 	61.8 ± 3.01 ^b	>100 ^b
2 	53.5 ± 1.76 ^b	>100 ^b
3 	99.3 ± 3.78 ^b	>100 ^b
4 	66.9 ± 1.19 ^b	>100 ^b
9 	24.9 ± 1.30 ^b	>100 ^b
10 	12.2	nd
5 	nd	nd
6 	nd	nd
7 	nd	nd
8 	nd	nd

^a Values are given with standard error.^b Source: Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrad, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A. Evaluation of Difluoromethyl ketones as Agonists of the γ-Aminobutyric Acid Type B Receptor. *Med. Chem.* **2013**, *56*, 2456–2465

3. Conclusion

In summary, eight fluorinated compounds were synthesized to be evaluated at the GABA receptors. Four difluoromethyl ketones were synthesized using a novel method involving the release of trifluoroacetate to extend the scope of the published procedure. The compounds were purified via flash column chromatography and the purity of the compounds was evaluated using ^1H NMR and ^{19}F NMR. Additionally, four monofluoromethyl ketones were synthesized using similar techniques to be biologically evaluated at the GABA_B receptor. The goal of the project was to determine if monofluoromethyl ketones have a greater potency than difluoromethyl ketones at the GABA_B receptor. Samples of monofluoromethyl ketones were sent for biological testing, but no results have been received at this time.

4. Experimental Details

2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one. A mixture of (Z)-4,4,4-trifluoro-3-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one (0.500 g, 1.88 mmol) and acetonitrile (12.5 mL) was treated with selectfluor (1.66 g, 4.70 mmol) at rt under argon. After 20 h, the reaction was diluted with ethyl acetate (125 mL) and filtered through Celite. The residue was concentrated *in vacuo*, dissolved in dichloromethane (50 mL) and washed with water (50 mL). The aqueous layer was extracted with dichloromethane (50 mL). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. The solid product was afforded in 92% yield: ¹H NMR (500 MHz, CDCl₃) δ 8.74 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.0 Hz, 1H), 7.61 (t, *J* = 7.1 Hz, 1H), 4.74 (s, 2H).

2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)propan-1-one, 1. A mixture of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.2 mmol), *p*-anisaldehyde (38 μL, 0.31 mmol), and LiBr (41 mg, 0.47 mmol) in THF (1 mL) was treated with triethylamine (22 μL, 0.16 mmol) dropwise. The reaction was stirred at rt for 10 min, and was quenched with saturated aqueous NH₄Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL × 5). The organics were dried over Na₂SO₄ and concentrated under reduced pressure. SiO₂ flash chromatography (3.5:1.5 hexanes/ethyl acetate) afforded the product as a solid in 77% yield: ¹H NMR (500 MHz, CDCl₃) δ 8.62 (s, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 7.97 – 7.84 (m, 2H), 7.65 (t, *J* = 7.0 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 5.39 (dd,

$J = 18.0, 5.9$ Hz, 1H), 3.81 (s, 3H), 2.99 (s, 1H).

3-Cyclohexyl-2,2-difluoro-3-hydroxy-1-(naphthalen-2-yl)propan-1-one, 2. A mixture of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.2 mmol), cyclohexanecarbaldehyde (38 μ L, 0.31 mmol), and LiBr (47 mg, 0.55 mmol) in THF (1 mL) was treated with triethylamine (86 μ L, 0.62 mmol) dropwise. The reaction was stirred at -78°C for 30 min, and was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL \times 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (9:1 hexanes/ethyl acetate) afforded the product as a solid in 84% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.70 (s, 1H), 8.08 (d, $J = 8.7$ Hz, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.90 (dd, $J = 12.2, 8.5$ Hz, 3H), 7.65 (dt, $J = 8.2, 1.2$ Hz, 2H), 7.58 (t, $J = 7.5$ Hz, 1H), 4.13 (dq, $J = 19.6, 6.1$ Hz, 1H), 2.43 (d, $J = 6.7$ Hz, 1H), 2.12–1.53 (m, 6H), 1.47–1.16 (m, 5H).

(4E,6E)-2,2-Difluoro-3-hydroxy-1-(naphthalen-2-yl)octa-4,6-dien-1-one, 3. A mixture of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.2 mmol), (2E,4E)-hexa-2,4-dienal (34 μ L, 0.31 mmol), and LiBr (47 mg, 0.55 mmol) in THF (1 mL) was treated with triethylamine (22 μ L, 0.16 mmol) dropwise. The reaction was stirred at rt for 10 min, and was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL \times 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (9:1 hexanes/ethyl acetate) afforded the product as a solid in 55% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.71 (s, 1H), 8.07 (d, $J = 8.6$ Hz, 1H), 7.98 (d, $J = 8.1$ Hz, 1H), 7.89 (dd, $J =$

11.0, 8.6 Hz, 2H), 7.65 (t, $J = 7.1$ Hz, 1H), 7.57 (t, $J = 7.9$ Hz, 1H), 6.45 (dd, $J = 15.3$, 10.5 Hz, 1H), 6.21 – 5.97 (m, 1H), 5.90 – 5.76 (m, 1H), 5.72 (dd, $J = 15.4$, 6.9 Hz, 1H), 4.85 (dt, $J = 14.7$, 6.9 Hz, 1H), 2.74 (s, 1H), 1.78 (d, $J = 6.5$ Hz, 3H).

(E)-2,2-Difluoro-3-hydroxy-1-(naphthalen-2-yl)oct-4-en-1-one, 4. A mixture of 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.3 mmol), (E)-hex-2-enal (37 μ L, 0.31 mmol), and LiBr (47 mg, 0.55 mmol) in THF (1 mL) was treated with triethylamine (22 μ L, 0.16 mmol) dropwise. The reaction was stirred at rt for 10 min, and was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL \times 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (9:1 hexanes/ethyl acetate) afforded the product as a solid in 45% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.71 (s, 1H), 8.08 (d, $J = 8.6$ Hz, 1H), 7.99 (d, $J = 8.1$ Hz, 1H), 7.90 (dd, $J = 11.9$, 8.5 Hz, 2H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.58 (t, $J = 7.6$ Hz, 1H), 5.96 (dt, $J = 14.2$, 6.7 Hz, 1H), 5.66 (dd, $J = 15.5$, 6.9 Hz, 1H), 4.78 (dq, $J = 13.0$, 6.5 Hz, 1H), 2.61 (d, $J = 5.6$ Hz, 1H), 2.10 (q, $J = 7.0$ Hz, 2H), 1.43 (q, $J = 7.3$ Hz, 2H), 0.91 (t, $J = 7.4$ Hz, 3H).

2,4,4,4-Tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one. A mixture of (Z)-4,4,4-trifluoro-3-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one (0.500 g, 1.88 mmol), water (6 mL) and acetonitrile (6 mL) was treated with selectfluor (0.665 g, 1.88 mmol) at rt under air. After 18 h, the residue was washed with water (50 mL). Saturated aqueous NaCl (10 mL) was added to the mixture and the product was extracted with dichloromethane (10 mL \times 5). The combined organics were dried over Na_2SO_4 and

concentrated under reduced pressure. The solid product was afforded in 88% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.61 (s, 1H), 8.02 (dd, $J = 7.7, 4.5$ Hz, 2H), 7.92 (dd, $J = 14.2, 8.4$ Hz, 2H), 7.68 (t, $J = 8.1$ Hz, 1H), 7.61 (t, $J = 7.5$ Hz, 1H), 5.87 (d, $J = 47.8$ Hz, 1H), 4.90 (s, 1H), 4.55 (s, 1H); ^{19}F NMR (376 MHz, CDCl_3) δ -83.9 (d, $J = 11.5$ Hz, 3F), -194.6 (dq, $J = 47.7, 11.2$ Hz, 1F).

2-Fluoro-3-hydroxy-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)propan-1-one, 5. A mixture of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.2 mmol), cyclohexanecarbaldehyde (40 μL , 0.33 mmol), and LiBr (72 mg, 0.82 mmol) in THF (1 mL) was treated with triethylamine (27 μL , 0.20 mmol) dropwise. The reaction was stirred at rt for 30 min, and was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL \times 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (3.5:1.5 hexanes/ethyl acetate) afforded the product as an inseparable mixture of diastereomers (dr = 1.78:1) in 23% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.41 (d, $J = 15.2$ Hz, 1H), 7.94 (dd, $J = 14.1, 9.2$ Hz, 2H), 7.91–7.85 (m, 2H), 7.63 (t, $J = 7.6$ Hz, 1H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.38 (dd, $J = 8.6, 3.9$ Hz, 2H), 6.87 (dd, $J = 12.4, 8.7$ Hz, 2H), 5.85–5.58 (m, 1H), 5.31 (d, $J = 22.5$ Hz, 1H), 3.76 (d, $J = 14.0$ Hz, 3H), 2.98 (s, 1H); ^{19}F NMR (376 MHz, CDCl_3) δ -188.9–-189.9* (m, 1F), -195.9 (dd, $J = 48.4, 21.3$ Hz, 1F). *Denotes minor diastereomer.

3-Cyclohexyl-2-fluoro-3-hydroxy-1-(naphthalen-2-yl)propan-1-one, 6. A mixture of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.2 mmol), *p*-

anisaldehyde (40 μ L, 0.3 mmol), and LiBr (50 mg, 0.6 mmol) in THF (1 mL) was treated with triethylamine (92 μ L, 0.66 mmol) dropwise. The reaction was stirred at rt for 10 min, and was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL \times 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (4:1 dichloromethane/hexanes) afforded the product as a solid in 57% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.58 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.90 (dd, J = 11.6, 8.5 Hz, 2H), 7.63 (t, J = 6.9 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 5.60 (dd, J = 47.7, 7.0 Hz, 1H), 4.06 (s, 1H), 2.46 (s, 1H), 1.97–1.54 (m, 6H), 1.46–1.11 (m, 5H); ^{19}F NMR (376 MHz, CDCl_3) δ –190.7 (dd, J = 47.8, 9.8 Hz, 1F).

(4*E*,6*E*)-2-Fluoro-3-hydroxy-1-(naphthalen-2-yl)octa-4,6-dien-1-one, 7. A mixture of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.2 mmol), (2*E*,4*E*)-hexa-2,4-dienal (38 μ L, 0.33 mmol), and LiBr (50 mg, 0.6 mmol) in THF (1 mL) was treated with triethylamine (23 μ L, 0.16 mmol) dropwise. The reaction was stirred at rt for 30 min, and was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL \times 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (9:1 hexanes/ethyl acetate) afforded the product as an inseparable mixture of diastereomers (dr = 15:1) in 40% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.55 (s, 1H), 7.99 (t, J = 8.8 Hz, 2H), 7.95 – 7.84 (m, 2H), 7.63 (t, J = 8.0, 6.9 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 6.36 (dd, J = 15.5, 10.3 Hz, 1H), 6.03 (t, J = 12.9 Hz, 1H), 5.86–5.47 (m, 3H), 4.78 (d, J = 21.1 Hz, 1H), 2.36 (s, 1H), 1.75 (d, J = 6.6 Hz, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ –194.2* (dd, J =

48.6, 15.0 Hz, 1F), -198.5 (dd, $J = 48.3, 21.7$ Hz, 1F). *Denotes minor diastereomer.

(*E*)-2-Fluoro-3-hydroxy-1-(naphthalen-2-yl)oct-4-en-1-one, 8. A mixture of 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-(naphthalen-2-yl)butan-1-one (50 mg, 0.2 mmol), (*E*)-hex-2-enal (38 μ L, 0.33 mmol), and LiBr (50 mg, 0.6 mmol) in THF (1 mL) was treated with triethylamine (23 μ L, 0.16 mmol) dropwise. The reaction was stirred at rt for 30 min, and was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 mL \times 5). The organics were dried over Na_2SO_4 and concentrated under reduced pressure. SiO_2 flash chromatography (4:1:0.5 dichloromethane/hexanes/ethyl acetate) afforded the product as an inseparable mixture of diastereomers (dr = 1.6:1) in 83% yield: ^1H NMR (500 MHz, CDCl_3) δ 8.54 (d, $J = 5.6$ Hz, 1H), 7.99 (t, $J = 8.4$ Hz, 2H), 7.95–7.85 (m, 2H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.60–7.54 (m, 1H), 5.94–5.49 (m, 3H), 4.71 (dd, $J = 16.9, 6.7$ Hz, 1H), 2.46 (s, 1H), 2.00 (d, $J = 6.8$ Hz, 2H), 1.40–1.30 (m, 2H), 0.84 (td, $J = 7.4, 3.6$ Hz, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -195.5 (dd, $J = 48.4, 16.3$ Hz, 1F), -198.4^* (dd, $J = 48.5, 21.0$ Hz, 1F). *Denotes minor diastereomer.

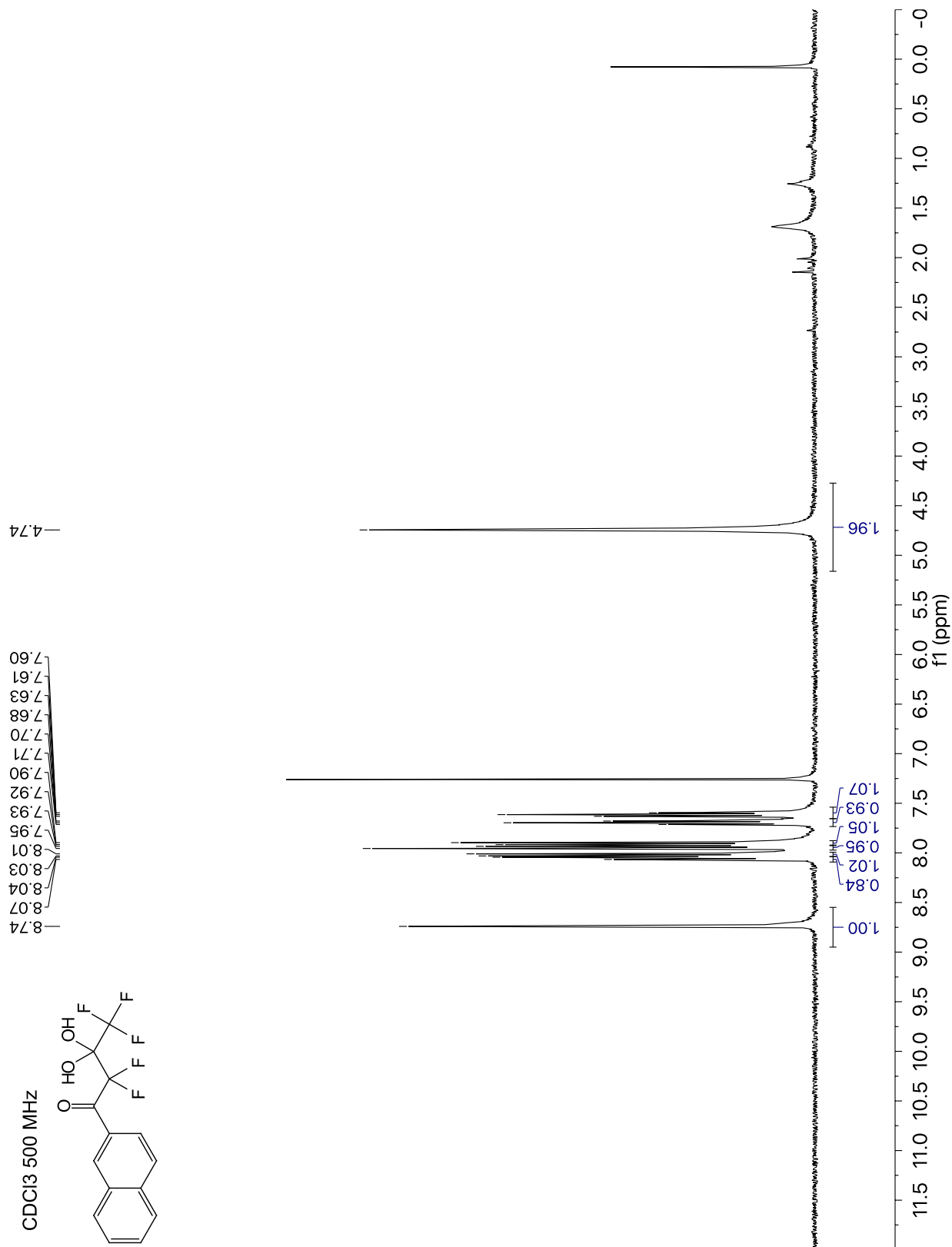
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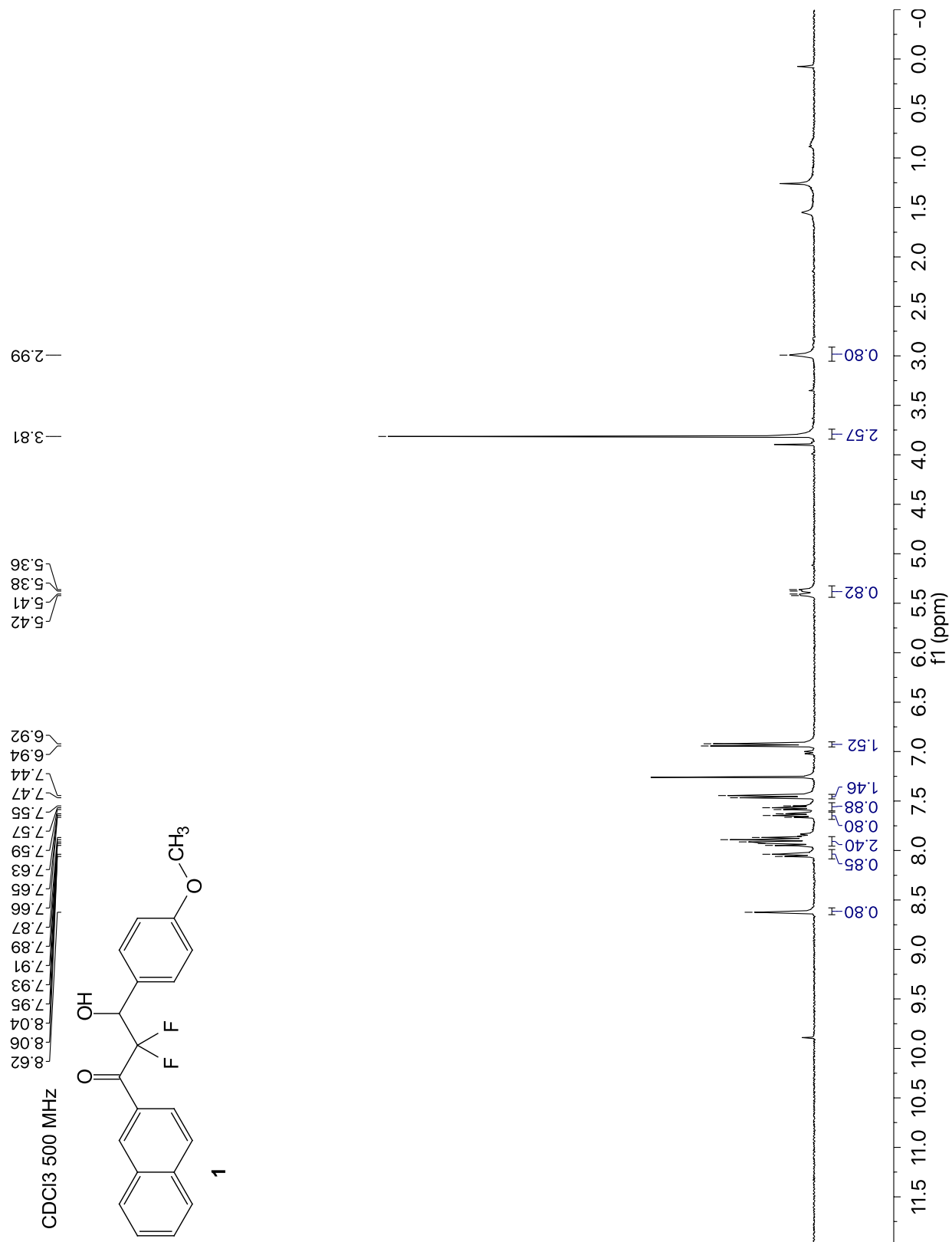
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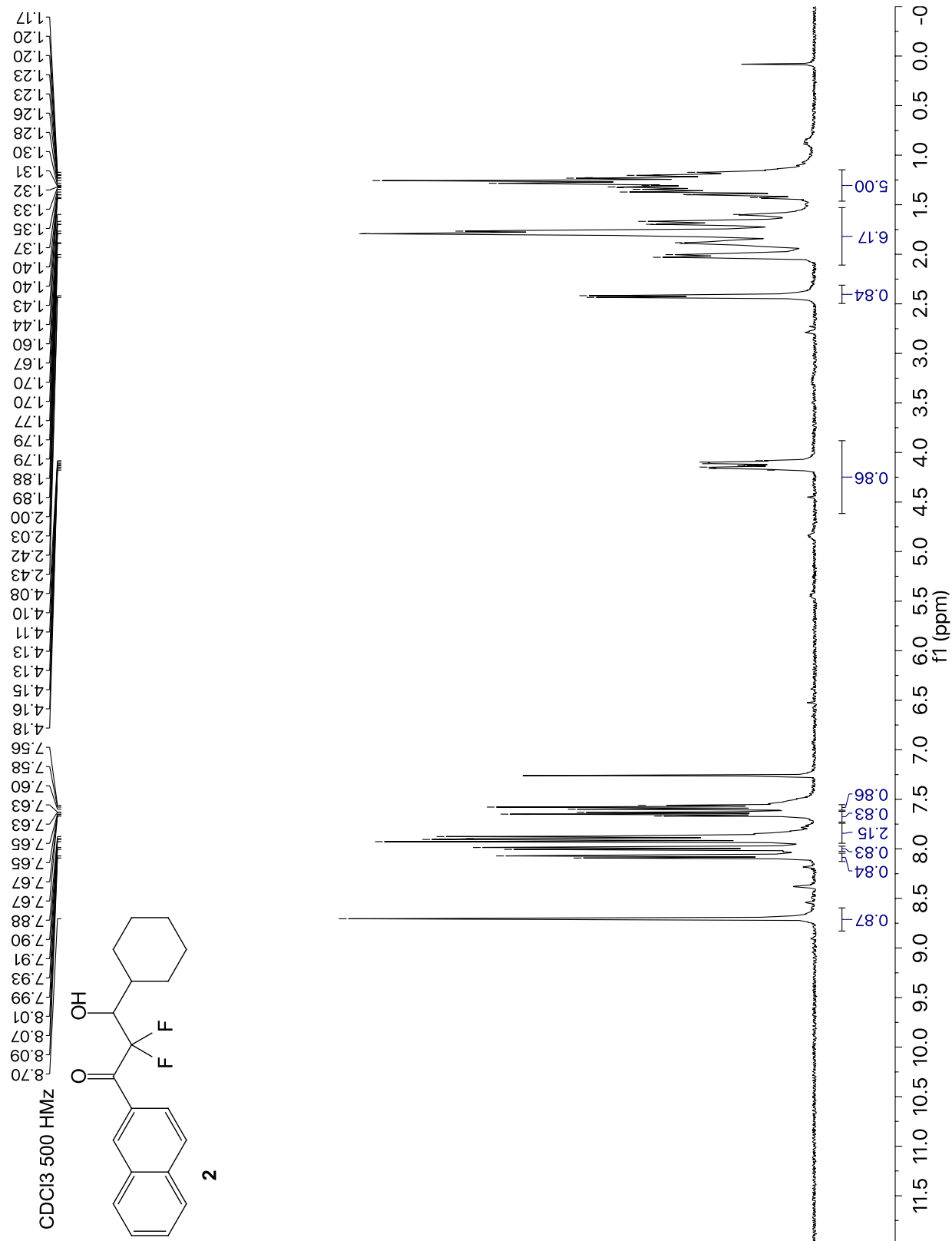
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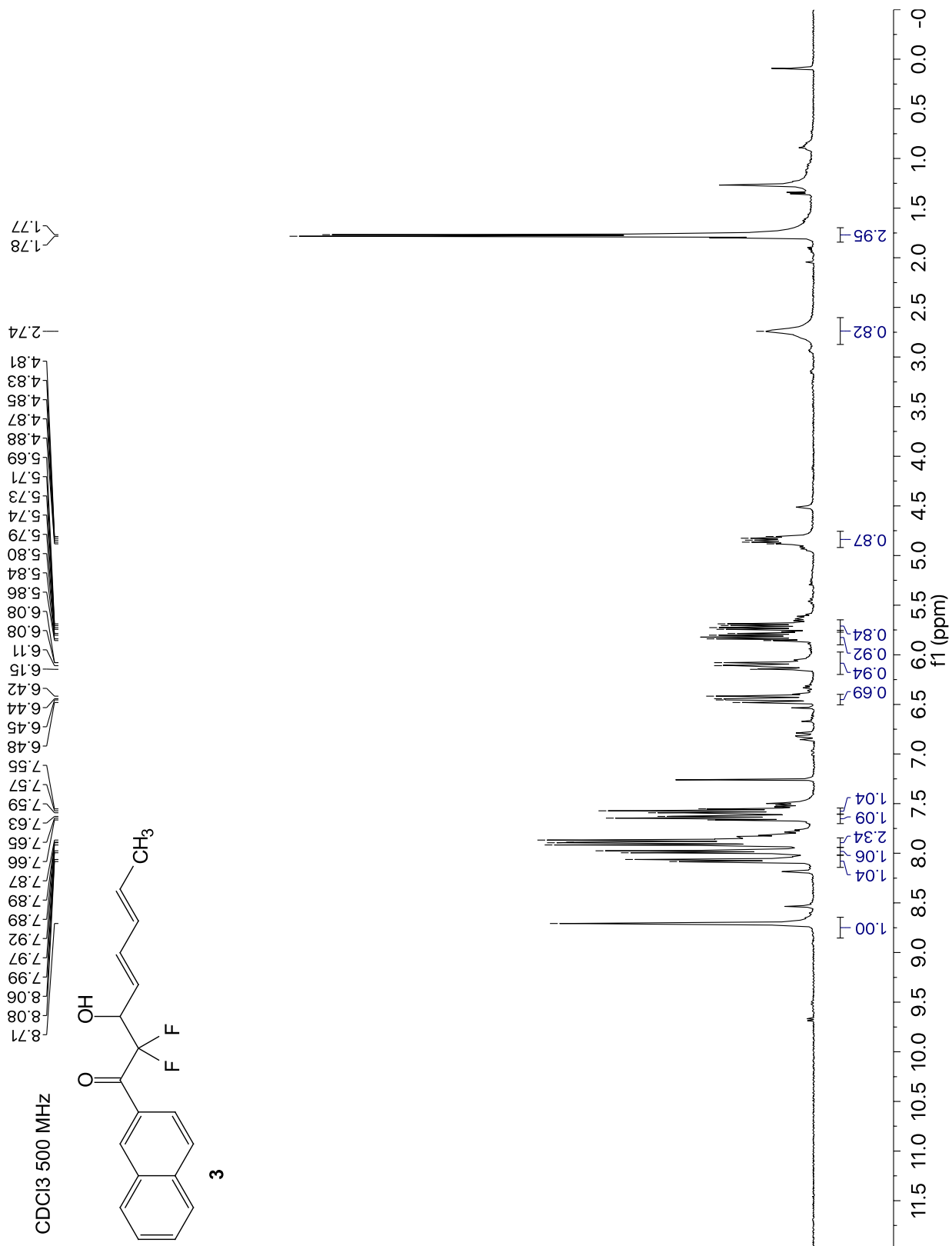
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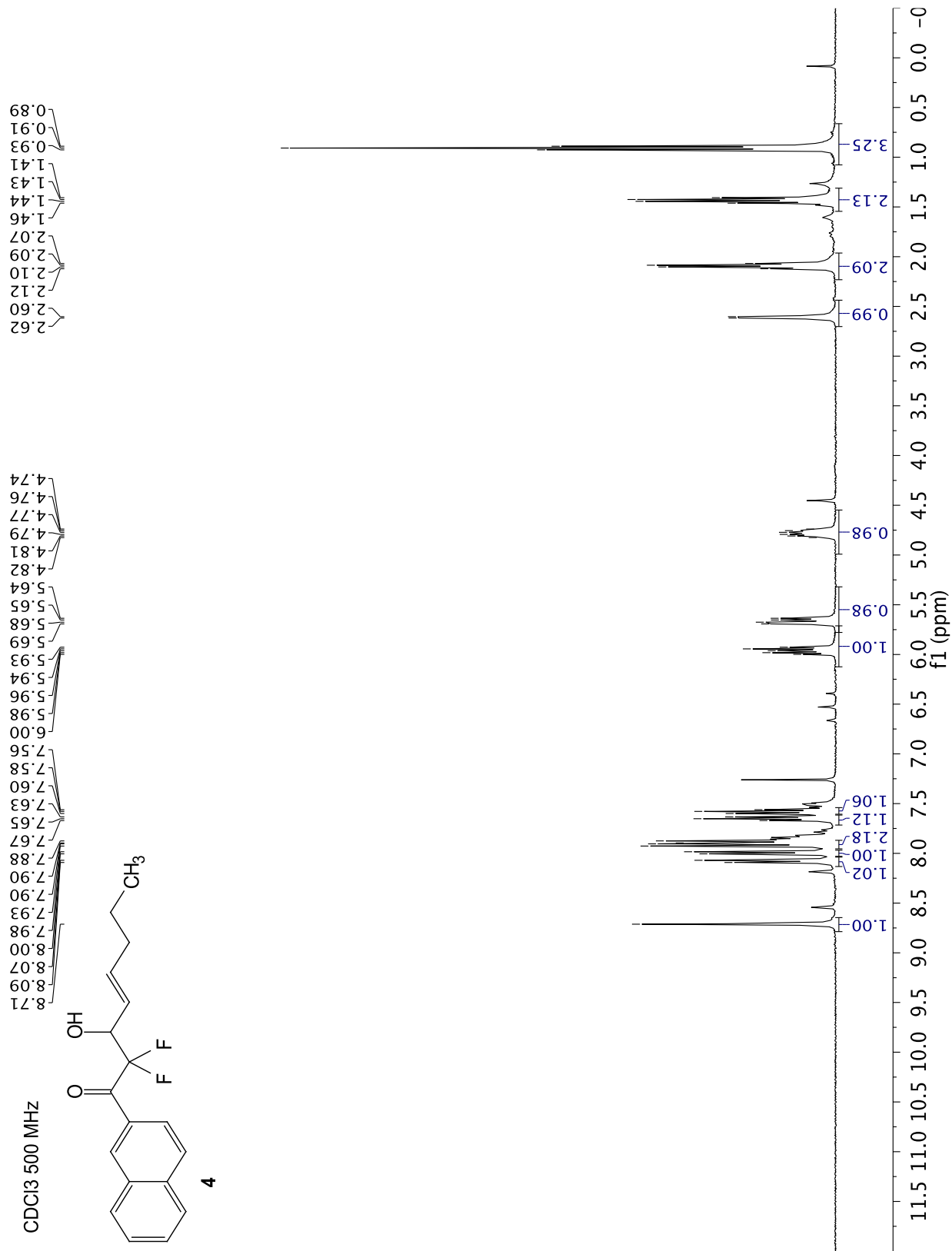
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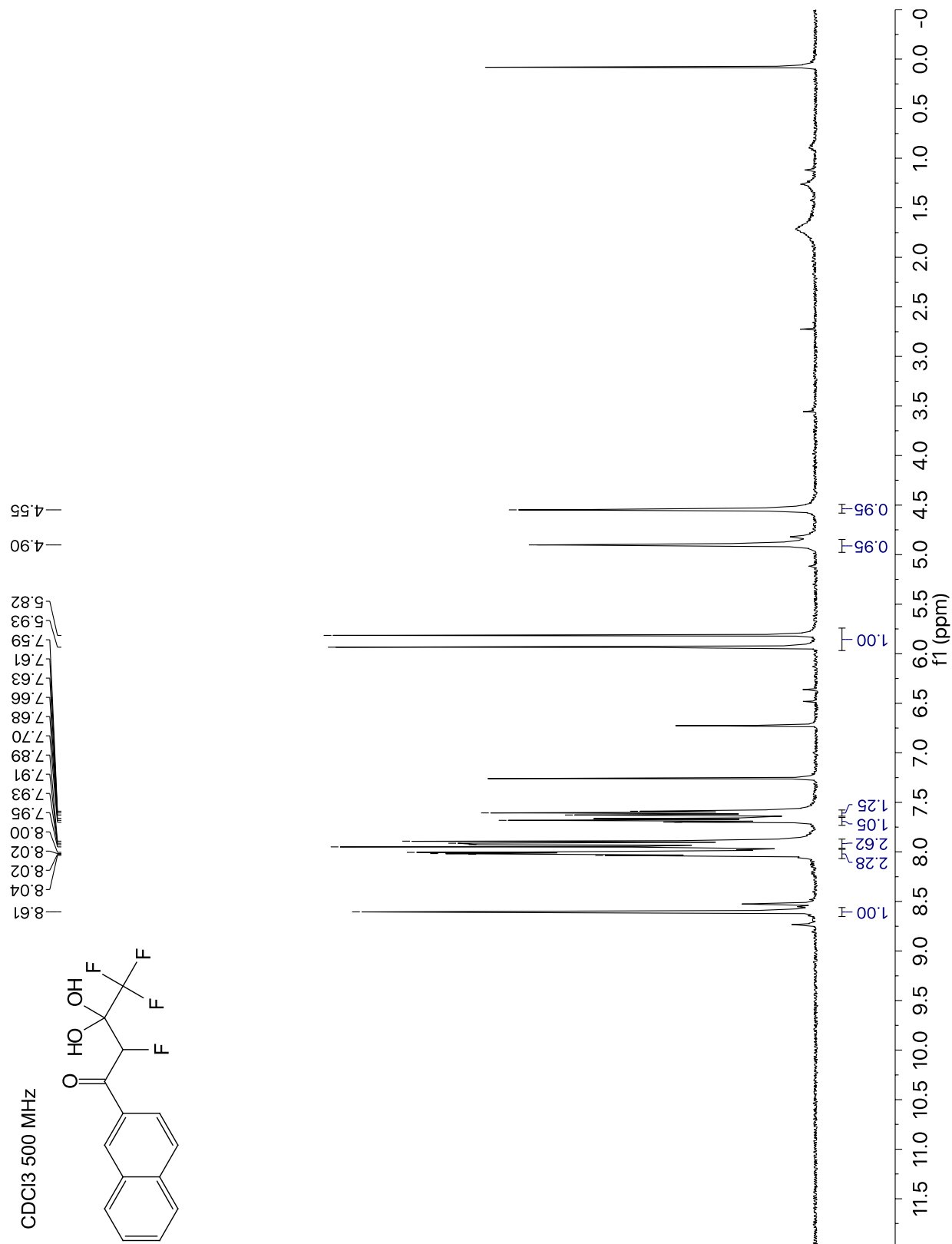


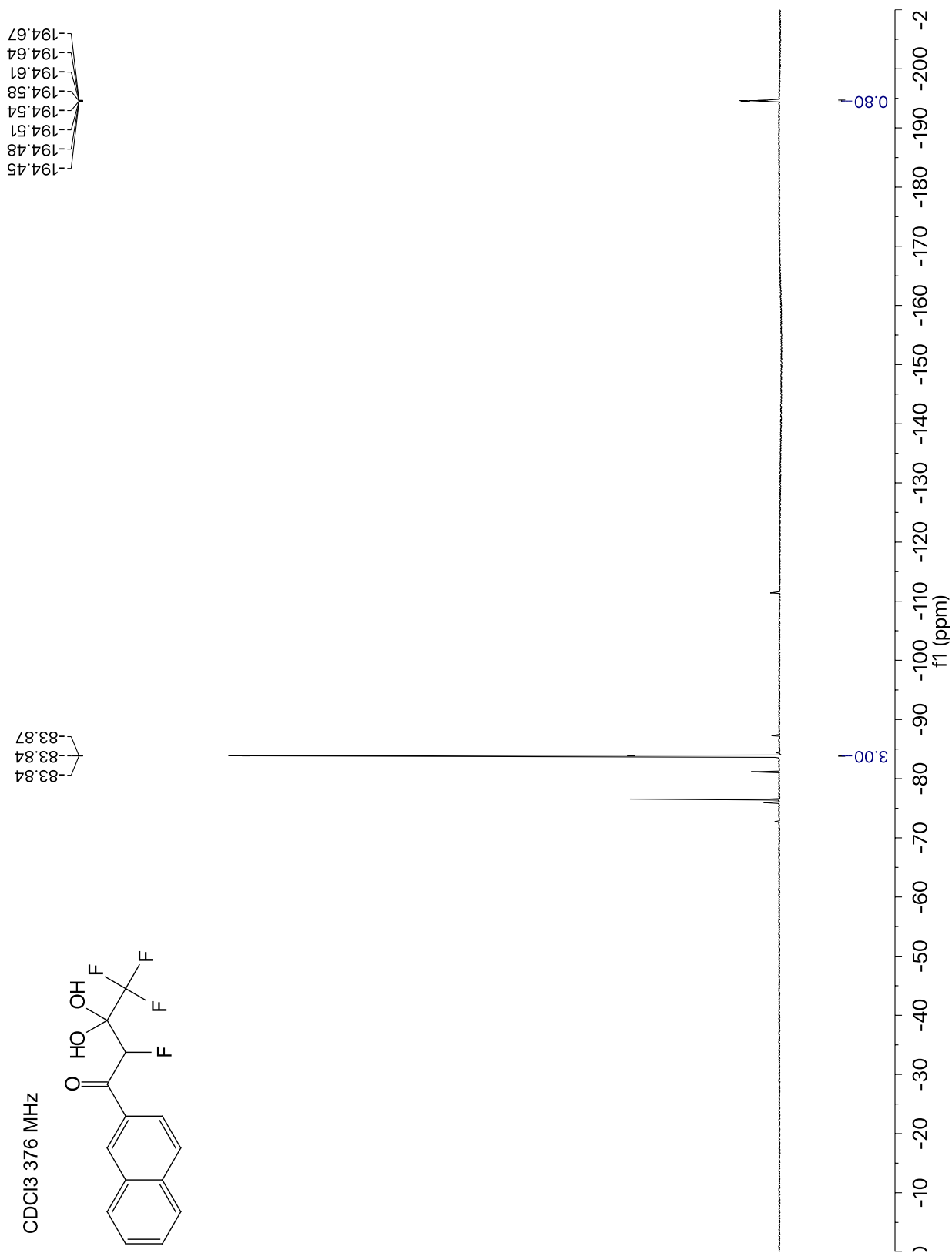


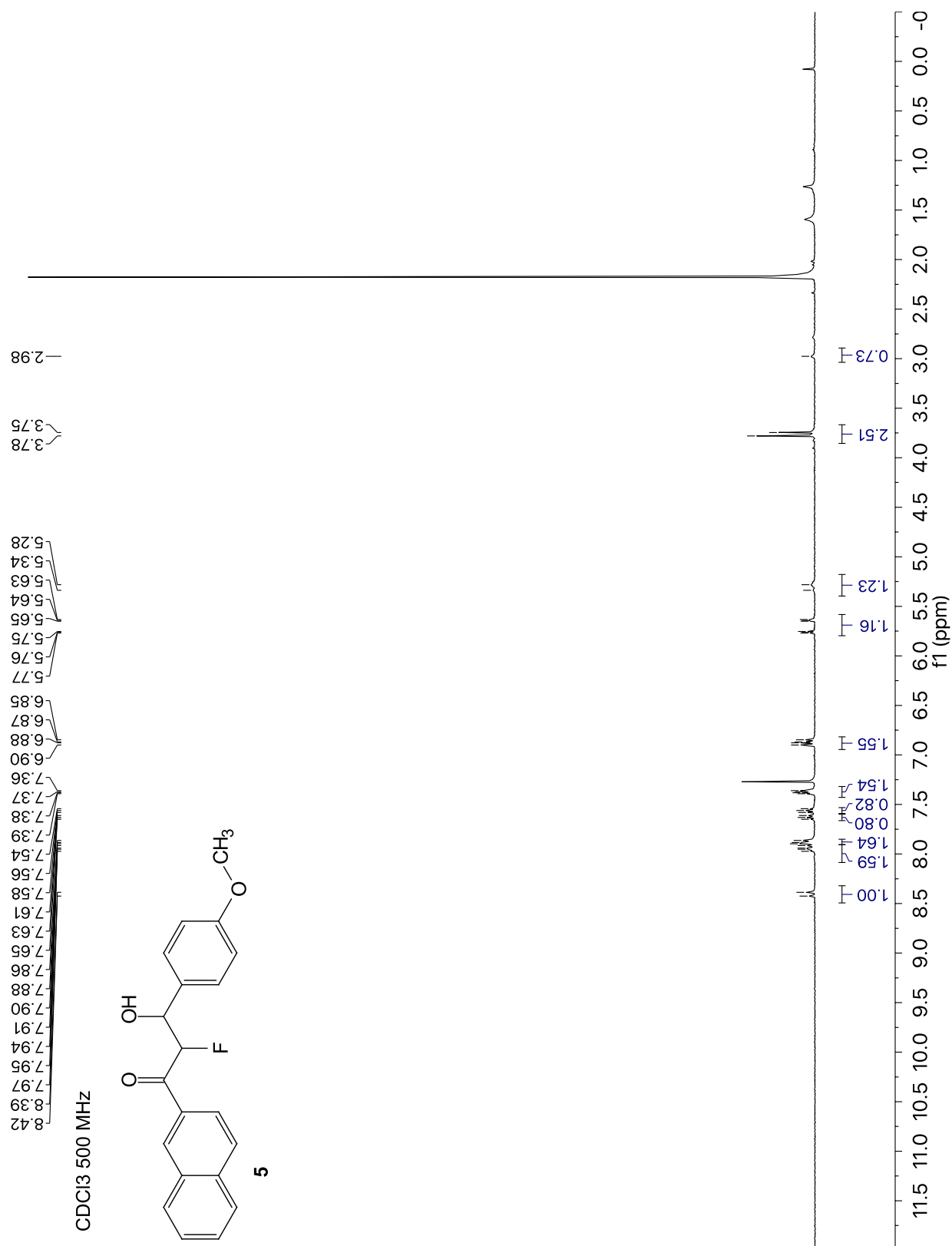




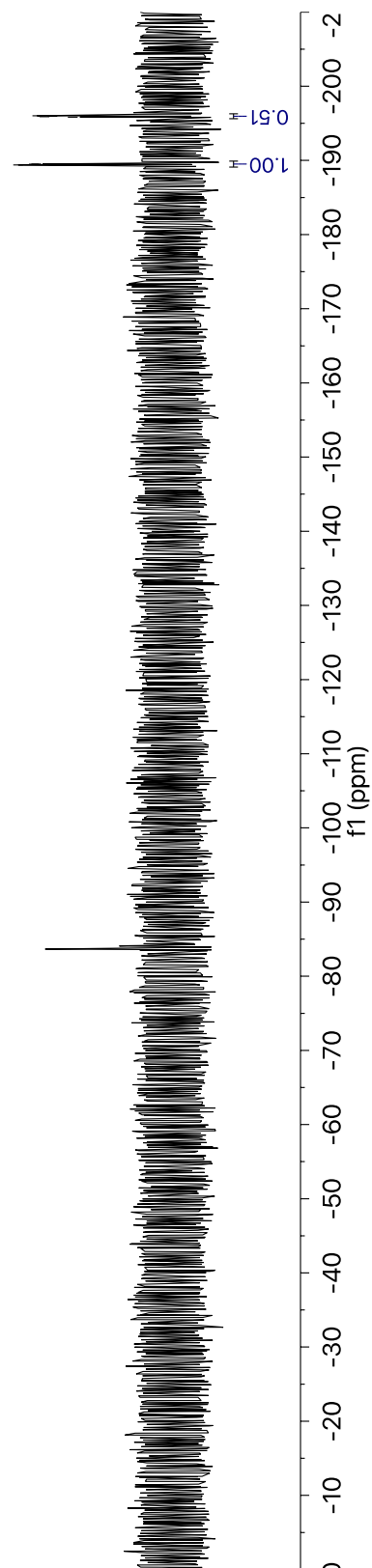
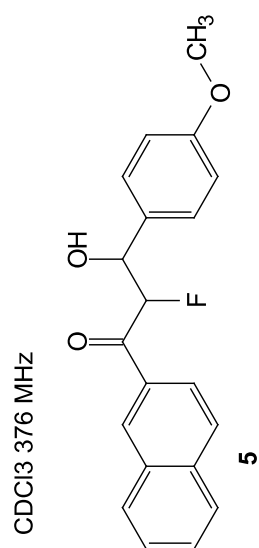


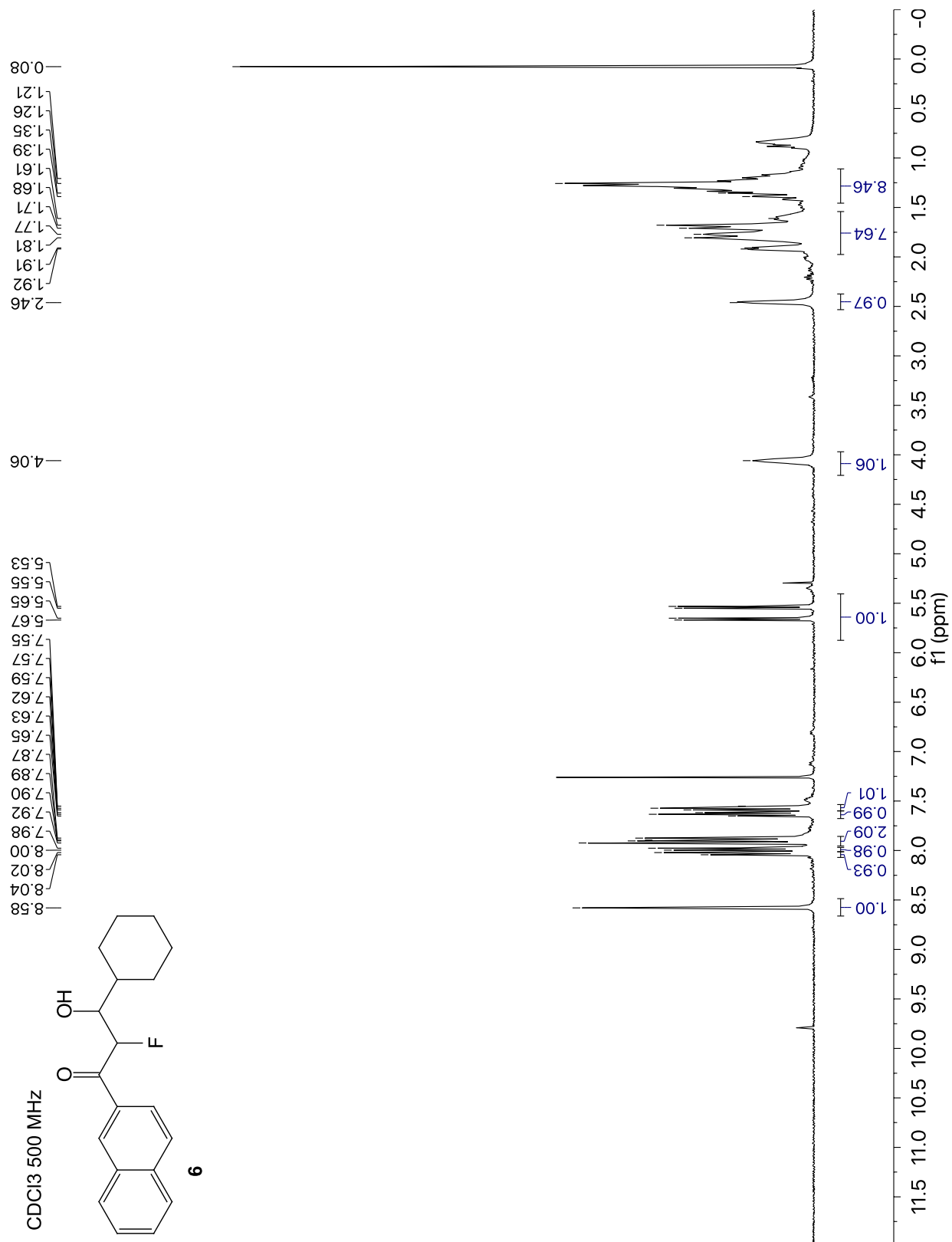


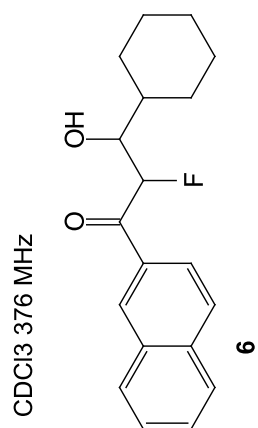




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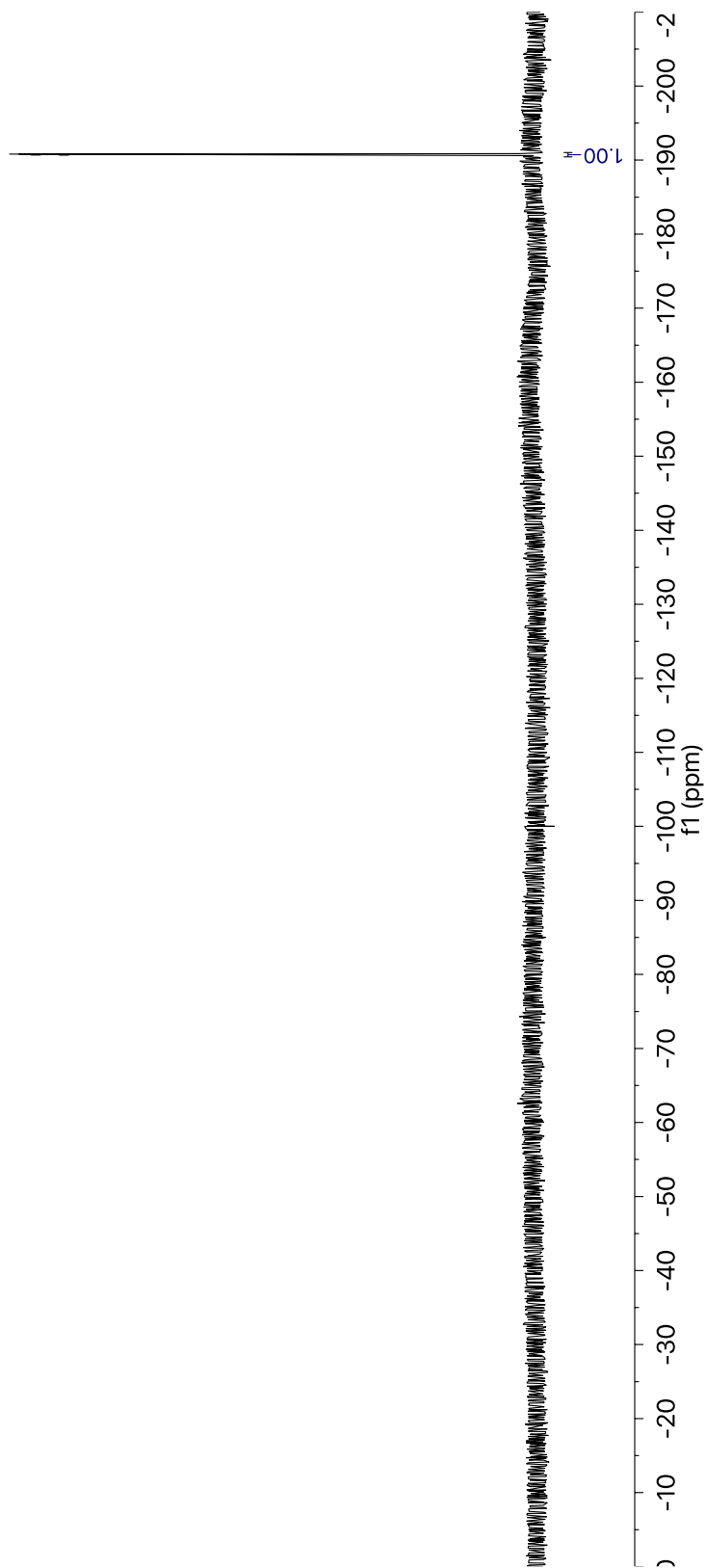


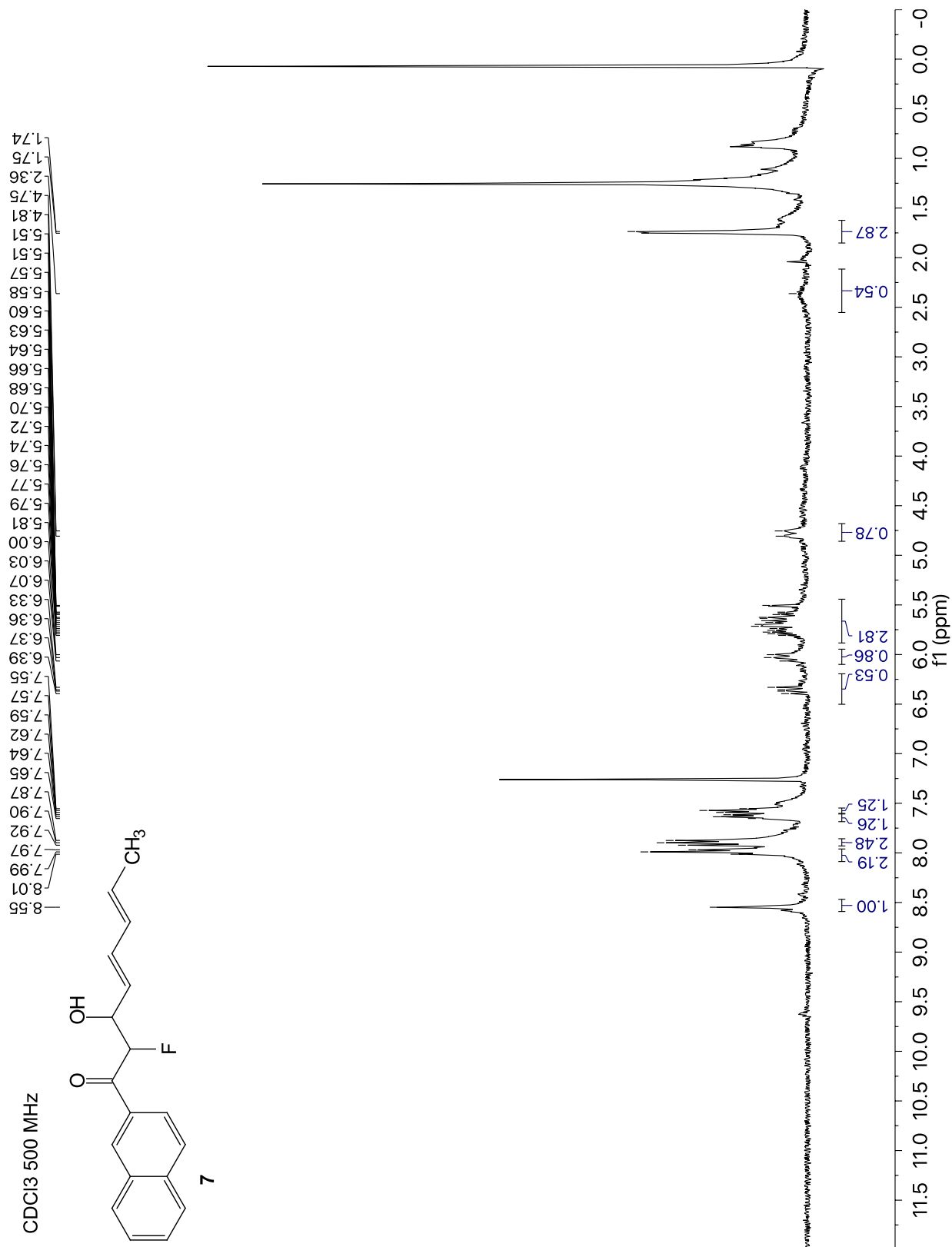


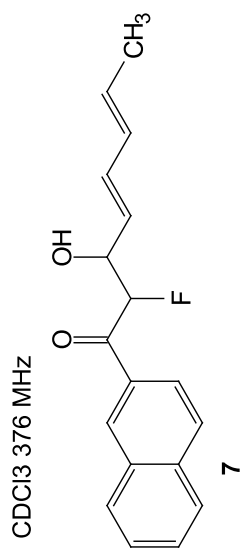


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